We claim:

1. A method for preferentially observing an exposed position of a macromolecule, comprising the steps of

(a) obtaining a sample comprising a macromolecule and a second molecule,

wherein the macromolecule is larger than 35 kiloDaltons and has a position that is exposed to the second molecule,

wherein a first proton is bound to the exposed position of the macromolecule, a second proton is bound to the second molecule, and the first proton can exchange with the second proton;

(b) applying a magnetic field to the sample, thereby magnetizing the first proton and the second proton;

(c) irradiating the sample with a pulse sequence that preferentially demagnetizes the protons of the macromolecule relative to the second proton;

(d) allowing the second proton to exchange with the first proton, whereby the relatively magnetized second proton becomes bound to the exposed position of the macromolecule; and

(e) detecting the magnetization from the second proton;

whereby the exposed position of the macromolecule is preferentially observed.

2. The method of claim 1, wherein the macromolecule is a polypeptide.

3. The method of claim 1, wherein the macromolecule is larger than about 50 kDa.

4. The method of claim 1, wherein the macromolecule is larger than about 75 kDa.

5. The method of claim 1, wherein the macromolecule is larger than about 100 kDa.

6. The method of claim 1, wherein the structure of the polypeptide has not been fully determined by an NMR technique.

7. The method of claim 1, wherein resonances for fewer than 5% of the amino acids of the protein have been assigned by NMR techniques.

8. The method of claim 1, wherein resonances for fewer than 10% of the amino acids of the protein have been assigned by NMR techniques.

9. The method of claim 1, wherein resonances for fewer than 50% of the amino acids of the protein have been assigned by NMR techniques.

10. The method of claim 1, wherein resonances for fewer than 75% of the amino acids of the protein have been assigned by NMR techniques.

11. The method of claim 1, wherein the second molecule is a protic solvent.

12. The method of claim 1, wherein the second molecule is water.

13. The method of claim 1, wherein the position on the macromolecule that is exposed to the second molecule comprises ^{15}N.

14. The method of claim 13, wherein the pulse sequence comprises an ^{15}N filter.

15. The method of claim 1, wherein the pulse sequence comprises the SEA pulse sequence.

16. The method of claim 1, wherein step (c) further comprises ^{15}N,^{1}H TROSY.

17. The method of claim 1, wherein the pulse sequence comprises the SEA-TROSY pulse sequence.

18. The method of claim 1, wherein step (d) occurs during a predetermined mixing time.

19. The method of claim 18, wherein the mixing time is between 25 and 300 ms.

20. The method of claim 18, wherein the mixing time is between 50 and 150 ms.

21. The method of claim 18, wherein the mixing time is between 80 and 120 ms.

22. The method of claim 1, further comprising the step of

(f) determining a heteronuclear correlation measurement for the sample, wherein one of the correlated nuclei is ^{1}H.

23. The method of claim 22, wherein the correlation measurement is an ^{15}N-^{1}H correlation measurement.

24. The method of claim 22, further comprising the step of

(g) determining a second heteronuclear correlation measurement between the correlated nuclei and a third nucleus.

25. The method of claim 24, wherein step (g) incorporates a HNCA measurement.

26. The method of claim 24, wherein step (g) incorporates a HNCACB measurement.

27. The method of claim 1, further incorporating a NOESY measurement.

28. The method of claim 1, wherein the macromolecule has a ligand bound to a position other than the exposed position.

29. The method of claim 1, wherein the second molecule is a ligand.

30. The method of claim 29, wherein the ligand is a natural ligand of the macromolecule.

31. The method of claim 29, wherein the ligand is a mimic of a natural ligand of the macromolecule.

32. The method of claim 29, wherein the sample is in a solvent, further comprising the step of irradiating the sample with a pulse sequence that preferentially demagnetizes the protons of the solvent.

33. A method for observing an exposed position in a macromolecule that binds a ligand,

wherein the macromolecule is larger than 35 kiloDaltons; has a plurality of protons bound to positions on the macromolecule that are exposed to the second molecule; and the exposed protons can exchange with protons of the second molecule;

comprising the steps of

(a) performing the method of claim 1 to a first sample comprising the macromolecule and a second molecule;

(b) performing the method of claim 1 to a second sample comprising the macromolecule and the second molecule, wherein the macromolecule is bound to a ligand; and

(c) detecting a perturbation in the second sample compared to the first sample;

thereby observing the exposed position in the macromolecule that binds the ligand.

34. The method of claim 33, wherein the perturbation is a chemical shift change.

35. The method of claim 33, wherein the perturbation is reduced signal intensity.

36. The method of claim 33, wherein the perturbation is differential proton exchange between the first and second sample.

37. The method of claim 33, wherein a second ligand is bound to the macromolecule in the first sample in a position other than the binding position of the first ligand.

38. A method for observing an exposed position in a macromolecule that binds a ligand,

wherein the macromolecule is larger than 35 kiloDaltons; has a plurality of protons bound to positions on the macromolecule that are exposed to the second molecule; and the exposed protons can exchange with protons of the second molecule;

comprising the steps of

(a) performing the method of claim 1 to a first sample comprising the macromolecule and a second molecule;

(b) performing the method of claim 1 to a second sample comprising the macromolecule, the second molecule and a ligand, wherein the second molecule and ligand alternatively associate with and dissociate from the macromolecule; and

(c) detecting a perturbation in the second sample compared to the first sample;

thereby observing the exposed position in the macromolecule that binds the ligand.

39. The method of claim 38, wherein the rate at which the ligand associates with the macromolecule is slower than or at most 10 fold higher than the rate at which the exposed protons of the macromolecule exchange with protons of the second molecule.

40. The method of claim 38, wherein the perturbation is a chemical shift change.

41. The method of claim 38, wherein the perturbation is reduced signal intensity.

42. The method of claim 38, wherein the perturbation is differential proton exchange between the first and second sample.

43. The method of claim 38, wherein a second ligand is bound to the macromolecule in the first sample in a position other than the binding position of the first ligand.

44. A method for observing a position in a macromolecule that is differentially exposed to two ligands,

wherein the macromolecule is larger than 35 kiloDaltons; has a plurality of protons bound to positions on the macromolecule that are exposed to a second molecule; and the exposed protons can exchange with protons of the second molecule;

comprising the steps of

(a) performing the method of claim 1 to a first sample comprising the macromolecule, the second molecule and a first ligand, wherein the second molecule and first ligand alternatively associate with and dissociate from the macromolecule;

(b) performing the method of claim 1 to a second sample comprising the macromolecule, the second molecule and a second ligand, wherein the second molecule and second ligand alternatively associate with and dissociate from the macromolecule; and

(c) detecting a perturbation in the second sample compared to the first sample;

thereby observing a position in the macromolecule that is differentially exposed in the presence of the first ligand compared to the second ligand.

45. The method of claim 44, wherein the rate at which the ligand associates with the macromolecule is slower than or at most 10 fold higher than the rate at which the exposed protons of the macromolecule exchange with protons of the second molecule.

46. The method of claim 44, wherein the perturbation is a chemical shift change.

47. The method of claim 44, wherein the perturbation is reduced signal intensity.

48. The method of claim 44, wherein the perturbation is differential proton exchange between the first and second sample.

49. The method of claim 44, wherein a second ligand is bound to the macromolecule in the first sample in a position other than the binding position of the first ligand.